Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

REVIEW ARTICLE

Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis

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To cite this article: Valent P, Escribano L, Broesby-Olsen S, Hartmann K, Grattan C, Brockow K, Niedoszytko M, Nedoszytko B, Oude Elberink JNG, Kristensen T, Butterfield JH, Triggiani M, Alvarez-Twose I, Reiter A, Sperr WR, Sotlar K, Yavuz S, Kluin-Nelemans HC, Hermine O, Radia D, van Doormaal JJ, Gotlib J, Orfao A, Siebenhaar F, Schwartz LB, Castells M, Maurer M, Horny H-P, Akin C, Metcalfe DD, Arock M. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. *Allergy* 2014; DOI:10.1111/all.12436.

Keywords
diagnostic algorithm; KIT D816V; mast cells; mastocytosis; tryptase.

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Accepted for publication 24 April 2014

DOI:10.1111/all.12436

Edited by: Hans-Uwe Simon

Abstract

Mastocytosis is an emerging differential diagnosis in patients with more or less specific mediator-related symptoms. In some of these patients, typical skin lesions are found and the diagnosis of mastocytosis can be established. In other cases, however, skin lesions are absent, which represents a diagnostic challenge. In the light of this unmet need, we developed a diagnostic algorithm for patients with suspected mastocytosis. In adult patients with typical lesions of mastocytosis in the skin, a bone marrow (BM) biopsy should be considered, regardless of the basal serum tryptase concentration. In adults without skin lesions who suffer from mediator-related or other typical symptoms, the basal tryptase level is an important parameter. In those with a slightly increased tryptase level, additional investigations, including a sensitive *KIT* mutation analysis of blood leucocytes or measurement of urinary histamine metabolites, may be helpful. In adult patients in whom (i) *KIT* D816V is detected and/or (ii) the basal serum tryptase level is clearly increased (>25–30 ng/ml) and/or (iii) other clinical or laboratory features suggest the presence of 'occult' mastocytosis or another haematologic neoplasm, a BM investigation is recommended. In the absence of *KIT* D816V and other signs or symptoms of mastocytosis

or another haematopoietic disease, no BM investigation is required, but the clinical course and tryptase levels are monitored in the follow-up. In paediatric patients, a BM investigation is usually not required, even if the tryptase level is increased. Although validation is required, it can be expected that the algorithm proposed herein will facilitate the management of patients with suspected mastocytosis and help avoid unnecessary referrals and investigations.

Mastocytosis is a heterogeneous group of disorders defined by an abnormal expansion and accumulation of clonal mast cells in one or multiple organs (1–9). Based on the organ system(s) involved, cutaneous mastocytosis, systemic mastocytosis (SM) or a localized mast cell tumour is diagnosed (1–9). The World Health Organization (WHO) classification includes several different categories of cutaneous mastocytosis and SM (10–13). The symptoms, course and survival vary greatly among patients in the various categories of mastocytosis (14–17). In patients with cutaneous mastocytosis and indolent SM (ISM), the prognosis (regarding survival) is excellent, whereas patients with advanced SM have a poor prognosis with a clearly reduced life expectancy (1–8, 11–17). These poor prognosis patients are diagnosed as having aggressive SM, mast cell leukaemia or SM with an associated haematologic non-mast cell lineage disease (SM-AHNMD) (1–8, 11–17). Patients with aggressive SM and mast cell leukaemia typically suffer from organ damage caused by mast cell infiltration, which may result in progressive cytopenia, ascites, malabsorption or hepatopathy (so-called C-Findings) (1–8, 11–17), and most of these patients lack skin lesions (Table 1).

Patients with mastocytosis may also complain about symptoms that can be caused by various mast cell-derived mediators. Some of these patients suffer from an IgE-dependent allergy (18–25). The symptoms recorded may be mild, but can also be severe or even life-threatening (18–25). Various organ systems, including the skin (pruritus and flushing), the gastrointestinal tract (peptic symptoms, cramping and diarrhoea) and the central nervous system (headache, depression, moods and cognitive symptoms), may be involved (1–8, 18–27). In a smaller group of these patients, a mast cell activation syndrome (MCAS) is recorded (18–24, 28). Finally, patients with SM may also suffer from osteopenia or osteoporosis (sometimes with bone fractures) and from the cosmetic consequences of the disease (18, 26, 29) (Table 1).

Adult patients with SM are often presenting with maculopapular (urticaria pigmentosa-like) cutaneous lesions, also referred to as mastocytosis in the skin (MIS) (1–8, 18). Therefore, MIS is an important diagnostic indicator of SM in adults (Fig. 1). On the other hand, it is important to state that the lack of cutaneous lesions (MIS) does not exclude SM (Fig. 1). Patients in whom no MIS is found are a diagnostic challenge. In these patients, symptoms are variable and often atypical, and the basal tryptase level may be relatively low. Some of these patients may suffer from an IgE-dependent allergy, including hymenoptera venom allergy (19–24). In the past few years, an increasing number of such cases, many of them without definitive signs or symptoms of mastocytosis or another myeloid neoplasm that could explain an increased tryptase level, have been referred to specialized centres. For these cases, general management recommendations and a diagnostic algorithm are lacking.

The European Competence Network on Mastocytosis (ECNM) has been created some time ago, with the aim of studying the aetiology and manifestations of mastocytosis and to improve diagnosis and therapy (30). In the current report, the ECNM proposes guidelines and an algorithm for patients with suspected (systemic) mastocytosis. A similar

Table 1 Clinical findings and symptoms in patients with mastocytosis

	Clinical findings/features in patients with					
	CM	BMM	ISM	SSM	ASM	MCL
Skin lesions (MIS)	+	–	+	+	–/+	–
Pruritus and/or flushing	+	–	+	+	–/+	–/+
Mediator-induced symptoms	+/–	+/–	+/–	+/–	–/+	–/+
Constitutional symptoms	–/+	–/+	+/–	+	+	+
Neurological problems	–/+	–/+	+/–	+/–	+/–	–/+
Splenomegaly	–	–	–/+	+	+/–	+/–
Lymphadenopathy	–	–	–	+/–	+/–	+/–
Osteopenia/osteoporosis*	–	+/–	+/–	+/–	–/+	–/+
Osteolysis	–	–	–	–	–/+	–/+
Malabsorption	–	–	–	–	–/+	–/+
Ascites	–	–	–	–	+/–	+/–
Bleeding	–	–	–	–	+/–	+/–
Haematologic problems	–	–	–	–	+	+

CM, cutaneous mastocytosis; BMM, isolated bone marrow mastocytosis; ISM, indolent systemic mastocytosis; SSM, smouldering systemic mastocytosis; ASM, aggressive systemic mastocytosis; MCL, mast cell leukaemia.

Score: +, in a majority (>50%) of patients; +/–, seen in a subset of patients (5–50%); –/+, rarely seen (1 to <5%); –, never or almost never seen (<1%).

*In several of these patients, bone fractures are found (29).

Abbreviations

AHNMD, associated haematologic non-mast cell lineage disease; BM, bone marrow; ECNM, European Competence Network on Mastocytosis; ISM, indolent systemic mastocytosis; MCAS, mast cell activation syndrome; MIS, mastocytosis in the skin; SM, systemic mastocytosis; WHO, World Health Organization.

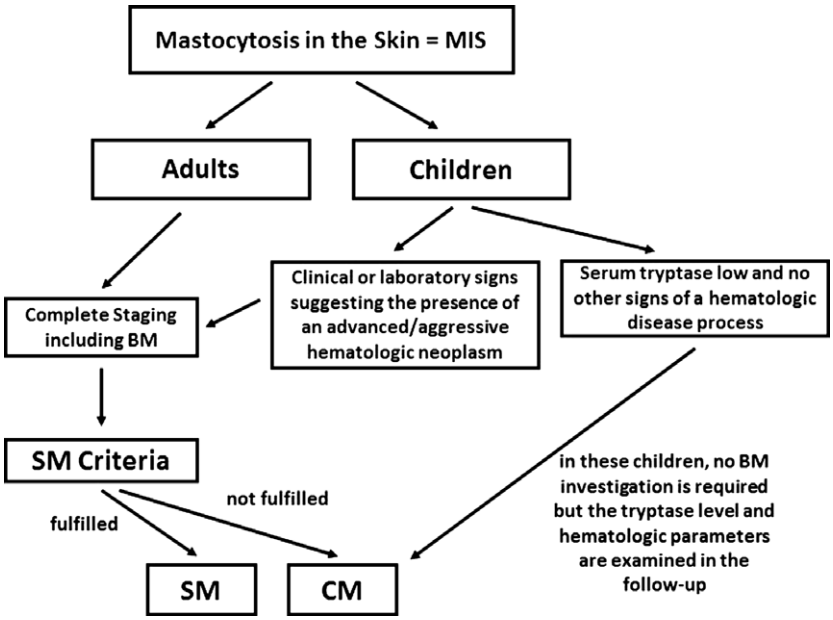

Figure 1 Algorithm for patients with suspected systemic mastocytosis and skin lesions. In all adult patients with documented mastocytosis in the skin (MIS), a complete staging, including a bone marrow (BM) investigation, is required. Based on the presence or absence of criteria for systemic mastocytosis (SM), the final diagnosis will be systemic mastocytosis (SM) or cutaneous mastocytosis (CM) in adults. In children with MIS, no BM investigation is required unless clinical and/or laboratory findings suggest the development of an advanced (aggressive) systemic haematologic neoplasm, such as the presence of organomegaly. In all childhood patients with MIS, the serum tryptase level and haematologic parameters should be monitored in the follow-up.

algorithm has recently been proposed by the Austrian Competence Network on Mastocytosis (AUCNM), which is a major partner and part of the ECNM (31). In addition, the proposed algorithm is related to the proposal of the Spanish Mastocytosis Network (REMA) and the recently published REMA score (32). The ECNM algorithm should facilitate diagnosis and management of patients with mastocytosis and should help avoid unnecessary referrals and investigations in daily practice.

Approach to patients with mastocytosis in the skin (MIS)

In childhood patients with MIS, a bone marrow (BM) investigation is not recommended unless serum tryptase levels are very high (>100 ng/ml) or the blood count and/or other clinical findings and symptoms suggest the presence of a haematologic neoplasm (18, 23) (Fig. 1). Sometimes, a *KIT* mutation is found in children (in the skin or blood) (33, 34), but even in these cases, no BM biopsy is performed. Rather, these patients are seen in the follow-up until cutaneous findings resolve in adolescence and no further findings appear.

In adult patients with MIS, a BM investigation is usually recommended, sometimes even in the absence of clinical symptoms (18, 23). In these patients, adequate histopathologic, cytologic, immunophenotypic and molecular studies should be performed (18, 23). Even if no *KIT* mutation is detectable in the skin or blood and even if the serum tryptase level is normal, a BM biopsy should be considered because the diagnosis of SM and SM variants (as opposed to cutaneous mastocytosis) has prognostic implications (18). However, the diagnosis of ISM usually has no immediate therapeutic implications. All patients have to be informed about potential implications and consequences before a BM examination is conducted. In patients in whom SM is diagnosed, a complete staging has to be performed (18). In those who do not agree to undergo a BM biopsy, the provisional diagnosis of MIS can be maintained without further staging investigations, unless clinical signs and symptoms argue for organ damage or the presence of a haematologic neoplasm (18). Otherwise, these patients are followed up in the same way as patients with ISM.

Patients with increased tryptase levels but no evidence of MIS

Patients without MIS in whom symptoms and laboratory parameters suggest the presence of mast cell activation or a clonal mast cell disease are an emerging challenge (23). In some of these patients, histamine-related symptoms or the presence of allergen-specific IgE can be documented (19, 24, 25). Others may suffer from unexplained osteoporosis (sometimes with fragility fractures), gastrointestinal symptoms or unexplained constitutional or neuropsychological symptoms (18, 23, 26–29) (Table 2). In several of the cases, a typical clinical constellation can be recorded: one example is severe

Table 2 Typical clinical features and symptoms recorded in patients with suspected systemic mastocytosis (SM) but without evidence of mastocytosis in the skin (MIS)*

Features/symptoms†	Findings increasing the likelihood of SM
Anaphylaxis with hypotension	Hymenoptera venom anaphylaxis (± specific IgE)
	Idiopathic anaphylaxis
	Other mast cell mediator-related symptoms
	Mast cell activation syndrome (MCAS)
	Increased basal tryptase level >20 ng/ml‡
Headache plus diarrhoea	Increased histamine levels (plasma, urine§)
	Responsive to histamine receptor blockers
	No GI tract disease found (endoscopy)
	No food allergy or other allergic disease
	Increased basal tryptase level >20 ng/ml§
Advanced osteopenia (T score < −2) or overt osteoporosis (± bone fractures) of unexplained aetiology	Male or post-menopausal female
	Increased basal tryptase level >20 ng/ml
Unexplained pruritus ± flushing	No skin disease found
	No internal disorder found
	Response to histamine receptor blocker
	Increased basal tryptase level >20 ng/ml‡
Unexplained neurological and/or psychiatric symptoms	No neurological or psychiatric disease
	No endocrine or vascular disease
	Increased basal tryptase level >20 ng/ml

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†If two or more of the symptoms listed are found, the likelihood increases that the patient is suffering from mastocytosis or a mast cell activation syndrome (MCAS).
‡In these patients, serum tryptase levels should be measured at least 24 h after complete resolution of all symptoms.
§Histamine metabolite levels are usually determined in urinary samples.

anaphylaxis after hymenoptera venom exposure combined with advanced osteopenia or osteoporosis in men. The recently established REMA score is a helpful tool that can assist in defining clinical patterns and constellations suggesting the presence of SM with sufficient precision and sensitivity, which in turn may justify a BM investigation (32). As mentioned, insect venom-induced anaphylaxis may be recorded in patients with SM without MIS (35, 36). Therefore, a BM examination is often recommended in these patients independent of the basal tryptase level, because a diagnosis of ISM or monoclonal MCAS modifies the insect venom immunotherapy, which should then (in case of ISM or MCAS) be lifelong (18, 20, 23). It is noteworthy that several of these patients have so-called (isolated) bone marrow mastocytosis (BMM), a condition characterized by small-sized mast cell aggregates in the BM and a normal or only slightly increased tryptase level (10–13). In patients without typical symptoms and slightly increased tryptase levels (but otherwise normal routine laboratory values and negative REMA score), we recommend performing *KIT* mutational analysis using peripheral blood leucocytes and a highly sensitive qPCR if the test is available (33, 37–39). If in such a patient, *KIT* D816V is detectable, a BM biopsy should be considered (Fig. 2). By contrast, in patients without a codon 816 mutation of *KIT*, a wait-and-watch strategy is recommended, unless other signs and symptoms would argue for the presence of SM (REMA score) or the presence of another BM disorder. Likewise, in some patients, levels of other mast cell mediators, such as urinary histamine metabolites (like methylhistamine or methylimidazole acetic acid, MIMA) and prostaglandin D2, may be increased, which may also assist in the evaluation of patients with suspected mastocytosis (25, 36, 40–42). In these patients, a BM examination may also be recommended, especially when other clinical or laboratory signs suggest the presence of SM. In other patients, the follow-up may reveal a steady increase in the basal tryptase level. In these patients, a BM examination is also recommended in order to exclude or reveal the development of SM or another myeloid neoplasm, such as a myelodysplastic syndrome. The algorithm proposed for adult patients with slightly increased tryptase levels without MIS is depicted in Fig. 2.

Diagnostic evaluation of patients with clearly increased tryptase levels

In adult patients who have a clearly increased basal serum tryptase level, a BM examination has to be considered, independent of laboratory findings or symptoms (18, 23). In fact, although rarely seen in healthy individuals, clearly increased tryptase levels (>25 or even >30 ng/ml) are almost exclusively recorded in patients with SM or another clonal BM disease, for example a myeloproliferative neoplasm, myelodysplastic syndrome or a myeloid leukaemia (5–9). Table 3 shows differential diagnoses that have to be considered in patients with increased tryptase levels. These differential diagnoses include, among others, chronic helminth infections and renal failure. An important pitfall to consider is the presence of (rare) heterophilic antibodies, which may interfere with the tryptase test and may produce false-positive test results, but the new generation of immunoassays should avoid this problem. Another important point to consider is that tryptase levels also increase during and shortly after an anaphylactic event (23, 43–45). In these cases, the tryptase level has to be re-examined at least 24 h after complete resolution of all signs and symptoms (23, 43–45). Further important questions to be addressed are the following: what is a 'clearly increased' tryptase level, and is there a tryptase cut-off level that would justify a BM biopsy even in the absence of additional symptoms and/or biochemical abnormalities that would suggest the presence of SM. The diagnostic cut-off level provided by WHO criteria (minor SM criterion) is 20 ng/ml (10–13). However, in recent years, it appears that more and more obviously healthy individuals have been identified with a

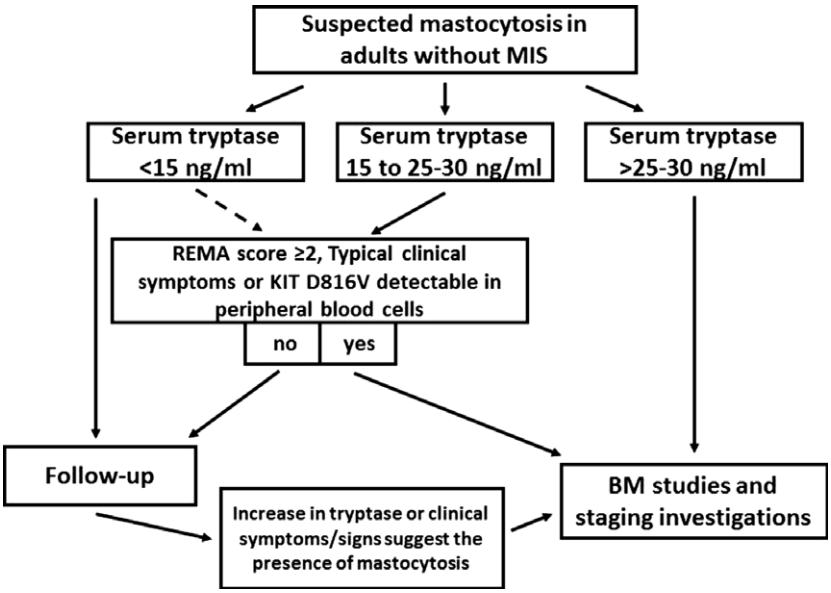

Figure 2 Algorithm for adult patients with suspected mastocytosis but no evidence of cutaneous involvement. In adult patients with suspected systemic mastocytosis (SM) without skin lesions, the basal serum tryptase level is an important initial parameter. In those who have a clearly increased tryptase level and/or a REMA score >2, a bone marrow (BM) biopsy is usually recommended. In those with normal or slightly increased tryptase level and a REMA score <2, it is helpful to examine peripheral blood cells for the presence of *KIT* D816V using a highly sensitive PCR if available. In patients in whom typical signs and symptoms (osteoporosis, histamine-induced symptoms, increased histamine metabolite excretion, unexplained anaphylaxis) or *KIT* D816V are detected, a BM examination should be performed. If no *KIT* mutation is detectable and symptoms are nonspecific, the patient will be examined during the follow-up. In patients with a normal tryptase level (<15 ng/ml), atypical symptoms and a REMA score <2, no *KIT* mutation analysis is required (dashed line), but the patient is observed in the follow-up. In countries and centres where no sufficient laboratory equipment and molecular assays are available, the algorithm has to be based on clinical parameters and tryptase levels in the follow-up. Bone marrow examinations should always include adequate histopathologic, cytomorphologic, immunophenotypic and molecular studies. This figure has been reproduced (with slight modifications) from Valent et al. (31) with permission.

slightly increased basal tryptase level, up to 25 or even 30 ng/ml. Based on these observations, we feel that a basal tryptase level that exceeds a certain threshold range (25–30 ng/ml) should be judged as 'clearly increased' in adults. In these cases, additional investigations, such as measurement of urinary histamine metabolites (if the test is available) or a BM investigation, may be justified even if the tryptase level remains constant in the follow-up and no other signs or symptoms indicative of SM or another myeloid neoplasm are found. The AUCNM has recently proposed a cut-off level of 30 ng/ml based on experience in more than 300 patients (31). The Spanish Network (REMA) has considered a level of 25 ng/ml as a reliable cut-off to propose a BM biopsy in adult patients (32).

In children, however, the approach is different compared with the algorithm in adults. In these patients, the likelihood of a systemic haematopoietic neoplasm (SM or other BM disease) is very low, regardless of the basal tryptase level. Based on this notion, a BM biopsy is not recommended in childhood patients with MIS even if the basal tryptase concentration is clearly increased (up to 100 ng/ml) (18, 23). In these patients, the diagnosis of cutaneous mastocytosis is established, unless clinical, radiologic or laboratory signs of a systemic disease are recorded (18). In those with a steady increase in basal tryptase level or with a massively increased serum tryptase level (>100 ng/ml) or other clinical or laboratory signs of a systemic neoplasm (e.g. organomegaly), a BM biopsy should be performed regardless of age (18).

Proposed follow-up investigations in patients with suspected mastocytosis

Management in the follow-up of patients with suspected mastocytosis depends on the overall condition and symptoms as well as on laboratory parameters. Basal serum tryptase levels should be measured at regular time intervals (at least once a year) in all patients, in order to assess the dynamics of this parameter. An increase in the tryptase level may point to disease evolution or progression, or the development of a non-mast cell lineage BM neoplasm, such as a myeloid leukaemia (46). Serum tryptase levels should also be measured in the follow-up in all patients with known SM for the reasons described above (18, 23). Moreover, peripheral blood counts and biochemical blood parameters should be determined in the follow-up in all SM patients. Depending on the clinical course and laboratory parameters, a repeated examination of the BM may be recommended. Likewise, a re-examination of the BM should be considered in patients in

Table 3 Differential diagnoses in patients with increased basal serum tryptase level but no evidence of mastocytosis in the skin (MIS)†

Diagnosis	Major cellular source of tryptase
Haematologic	
Systemic mastocytosis (SM)	Neoplastic mast cells
Chronic myeloid leukaemia (CML)	Neoplastic (immature) basophils
Chronic eosinophilic leukaemia (CEL)	Neoplastic mast cells
Chronic basophilic leukaemia (CBL)	Neoplastic (immature) basophils
Acute basophilic leukaemia (ABL)	Neoplastic (immature) basophils
Acute myeloid leukaemia (AML)	Blasts
Myelodysplastic syndrome (MDS)	Blasts, basophils, mast cells
Myeloproliferative neoplasm (MPN)	Blasts, basophils, mast cells
MDS/MPN overlap neoplasm	Blasts, basophils, mast cells
Myelomastocytic leukaemia (MML)	Blasts and neoplastic mast cells
MPN-eo* with abnormal *PDGFR*	Neoplastic mast cells
Non-haematologic reactive	
Allergic reaction‡	Mast cells
Mast cell activation syndrome (MCAS)‡	Mast cells
Atopic disorders	Mast cells
Chronic urticaria	Mast cells
Chronic inflammatory disease (CID)	Mast cells
Chronic helminth infection	Mast cells
Others/pitfalls	
Renal failure	Mast cells
Normal healthy individual§	Mast cells
False-positive test result¶	–
Genetic syndromes**	Mast cells

*MPN-eo: myeloproliferative neoplasm with eosinophilia.

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‡Transient increase in tryptase.

§About 1–3% of the healthy population present with increased basal tryptase level (>15 ng/ml).

¶False-positive results have previously been discussed as being related to the presence of heterophilic antibodies. The new generation of immunoassays should avoid this problem.

**Recently, rare genetic syndromes have been associated with increased tryptase and atopy (51).

whom the basal serum tryptase level increases constantly over time and/or the *KIT* mutation D816V becomes detectable in blood leucocytes.

In paediatric patients with suspected SM (with or without MIS), serum tryptase levels and other laboratory parameters should also be recorded in the follow-up. At least serum tryptase levels may correlate with disease severity in these patients (47, 48). An unresolved question is whether these parameters should still be measured after all skin lesions have disappeared in adolescence. In those patients in whom serum tryptase levels are normal and no other signs or symptoms remain, no further follow-up may be required. In all other patients, it may be preferable to measure blood counts and the serum tryptase level in the follow-up. In those patients in whom cutaneous lesions persist into adulthood, a BM investigation should be considered (18, 23). Whereas children with cutaneous mastocytosis are usually seen by a dermatologist or paediatrician, adult patients should be managed and followed up in a multidisciplinary manner, involving specialists in dermatology, haematology/oncology, and allergy/immunology who have major expertise with mastocytosis.

Future considerations and summary

Suspected mastocytosis in patients with atypical symptoms and borderline findings is an emerging diagnostic challenge, especially when the physician is inexperienced in the field of mast cell diseases, no skin lesions are present and the basal tryptase level is slightly increased or normal. Highly sensitive mutational analysis enabling the detection of *KIT* D816V in peripheral blood leucocytes is a potentially useful noninvasive test in these patients, particularly when they do not meet the REMA criteria. Demonstration of *KIT* D816V in blood cells is suggestive of SM, which needs to be confirmed by a thorough BM examination with adequate histopathologic, cytomorphologic, immunophenotypic and molecular studies. Additional staging investigations are also performed in these patients in order to establish a correct final diagnosis. The algorithms and recommendations of the ECNM should provide a valuable guideline for the management of patients with suspected SM and should assist in reducing unnecessary referrals and staging investigations, including BM studies. In the near future, additional markers and genetic testing (49–51) will be available and should further improve diagnostic algorithms.

Author contributions

All authors contributed equally by discussing data, literature material and case reports during the project period (October 2011 and October 2013). All authors contributed to designing the final concept and algorithms and to writing the manuscript. All authors approved the final version of the document.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Funding

This work was supported in part by the Austrian Science Funds (FWF) Project SFB F4611 and SFB F4704-B20 and the Division of Intramural Research, NIAID.

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